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Expert Panel on Drug Effects (EPDE)[3)]

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with a proposal for an IFCC Recommendation

Drug Interferences and Drug Effects in Clinical Chemistry

Part 5. Laboratory Tests during Clinical Trials

Prepared for publication[4)] *by*

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Preface

This paper ist the fifth of a series of Recommendations on Drug Interferences and Drug Effects in Clinical Chemistry. Others deal with:

Part 1. The basic concepts (1)
Part 2. Guidelines for evaluation of analytical interference (2)
Part 3. Evaluation of biological effects of drugs
Part 4. Clinical laboratory tests on laboratory animals during toxicity studies
Part 6. Laboratory tests in monitoring drug administration
Part 7. Data banks

The published documents should be consulted prior to the reading of the present part for a thorough understanding.

Contents

1. Introduction

Drugs administered during clinical trials may influence the laboratory test results observed in healthy subjects or in patients suffering from the illness the drug is intended to treat. These modifications may result from the pharmacological action and/or toxic effects of the drug candidate, or secondary drug effects.

Clinical trials are studies designed to discover and document drug efficacy and safety and to define drug pharmacology and bioavailability (3). Such trials require careful and thorough consideration of ethical issues governing their conduct.

Clinical trials are frequently divided into three or four phases (4):

Phase I clinical trials enroll small numbers of healthy volunteers or patients. Such trials define the tolerance of a drug candidate in the range of doses likely to be administered during therapy. Drug metabolism and pharmacokinetics in human are also studied during these trials.

Phase II clinical trials, usually conducted on up to 100 patients, allow for continued pharmacokinetic and toxicological studies of the drug candidate, under the specific physiological conditions induced by the illness. This phase also aims to demonstrate pharmacological activity in patients suffering from the illness the product is intended to treat and to allow an initial assessment of the therapeutic efficacy.

Phase III clinical trials require the participation of multiple institutions and enroll large numbers of patients. These trials compare the drug candidate to reference compounds of known therapeutic value or to placebo. The purpose of these trials is to document the efficacy of the drug candidate in comparison to a reference compound or placebo and to document the adverse effects caused by the drug candidate.

Phase IV clinical trials refer to studies performed after a drug has been approved for marketing in a particular country. These trials are designed to discover new indications, document safety and efficacy of new formulation, and provide surveillance of a drug as it becomes widely available to a population.

2. Choice and interpretation of laboratory tests during clinical trials

2.1 Choice of laboratory tests

During clinical trials, laboratory tests are performed with the aim of:

- Assessing the initial condition of subjects who will receive the drug candidate being studied. Laboratory tests, along with medical history, physical examination, and ancillary clinical testing provide criteria for selecting subjects to be enrolled in a clinical trial (inclusion or exclusion criteria).
- Documenting the possible beneficial effect induced by the drug candidate.
- Identifying the toxicity of the drug candidate which then allows evaluation of the risk: benefit ratio (risk due to therapy/benefits expected from therapy).
- Identifying secondary biological effects thus contributing to a better understanding of the effects of the drug candidate in human.

These objectives guide the choice of laboratory tests required for an individual clinical trial. Particular attention is paid to the chemical family and pharmacological class of the product tested and to results already obtained in animal toxicology studies. The specificity[5]) (3) of tests and especially their sensitivity[6]) (4) are taken into consideration.

2.2 Performance and interpretation of laboratory tests

Correct performance of specimen collection and processing techniques as well as test procedures are required to minimize sources of analytical variations. The interpretation of results should take both reference intervals and physiological variations into account. The results should be evaluated with appropriate controls, each subject being his own control whenever possible. Any significant variations observed should be compared to observations made during clinical studies and preclinical toxicological studies in animals, and to information previously acquired on the population under consideration (healthy or diseased subjects). Test result variations caused by analytical procedures themselves (i. e., drug interference, assay malfunction) should be taken into consideration. The variations observed in relationship to the

[5]) Specificity is "probability that test result will be negative when the disease is not present"

[6]) Sensitivity is "probability that test result will be positive when the disease is present"

drug candidate's administration schedule (dose, means of administration, duration of treatment, associated medications...), its metabolism and its pharmacokinetics must also be considered. It would be useful to check the analytical interferences of the analyte at the highest peak of drug concentration during clinical trials.

3. Factors influencing the choice and interpretation of laboratory tests for each phase of clinical trials

3.1 Phase I and II

As much information that is possible must be collected during Phase I and II clinical trials in order to define and interpret the large number of variables observed in the population studied. The following test profiles should be performed:

- An overall test profile designed to define the general state of health of those volunteers included in the study (Table 1).
- The test profile normally performed for the diagnosis and treatment of the disease involved (Tables 1 and 2).
- Test profiles related to functions which appear to have been influenced by the drug at the time of the first toxicological studies in animals (Table 2), particularly hepatic and renal function profiles which, if affected, may modify the substance's pharmacological profile. The eventual particular sensitivity of certain subjects (for example, children or old persons) must be taken into consideration.

Specimens should be collected prior to drug administration for baseline laboratory determinations. An aliquot of the specimens should be stored to permit additional testing which may prove necessary or desirable at a later date.

The frequency of blood sampling depends upon the half-life of the drug candidate being studied as determined by preclinical trials in animals and humans.

If the drug is administered as a single dose, specimen collection should be performed at regular interval(s) and should be close to the biological half-life of the active drug (or metabolite). If the drug is administered in multiple doses, successive series of samples should be taken at regular intervals and should depend on the duration of drug administration, the biological half-life of the active drug (metabolite) and previous clinical laboratory data obtained. In addition, a blood sample should be collected at halfway through the duration of the drug administration.

A final series of specimens are collected either when it is known that the drug or active metabolite administered are no longer present in the subject. Should one or more abnormal laboratory test results be discovered, then repeat clinical laboratory assessments should be performed until all abnormal results return to control or baseline levels.

The interpretation of results should be done according to the rules previously stated. In particular, the possibility of an analytical interference must be taken into account for specimens collected when the blood level of the active drug (or metabolite) is high (Part 2).

Tab. 1. Laboratory tests, useful for clinical trials[1])

Haematology
B-Haemoglobin, substance concentration
B-Leukocytes, number concentration
B-Leukocyte differential count
B-Platulocytes (Thrombocytes), number concentration
B-Erythrocytes, volume fraction (Haematocrit)
B-Erythrocytes, number concentration
B-Sedimentation reaction
Haemostasis
Pt-Bleeding time
P-Prothrombin time
P-Activated partial thromboplastin time
Blood chemistry
P,S-Alanine aminotransferase, catalytic activity concentration
P,S-Aspartate aminotransferase, catalytic activity concentration
P,S-Alkaline phosphatase, catalytic activity concentration
P,S-γ-Glutamyltransferase, catalytic activity concentration
P,S-Bilirubin, substance concentration
P,S-Cholesterol, substance concentration
(fPt) P,S-Triglyceride, substance concentration
P,S-Protein, mass concentration
P,S-Albumin, mass concentration
(fPt) B,P-Glucose, substance concentration
P,S-Urate, substance concentration
P,S-Carbamide (Urea), substance concentration
P,S-Creatininium (Creatinine), substance concentration
P,S-Sodium ion, substance concentration
P,S-Potassium ion, substance concentration
Urinalysis
dU-Volume
U-Density (Osmolality)
dU=Albumin, amount of mass
dU-Glucose, amount of substance
U-Acetoacetate, arbitrary concentration
U-Haemoglobin, arbitrary concentration
Routine urinary cytological examination

[1]) Abbreviations

System	Prefix
B-Blood	d-24 hour
P-Plasma	f-Fasting
S-Serum	t-Time
Pt-Patient	
U-Urine	

Tab. 2. Laboratory tests, according to organs and functions, useful for clinical trials

Blood Haemostasis

B-Haemoglobin, substance concentration
B-Leukocytes, number concentration
B-Leukocyte differential count
B-Erythrocytes, volume fraction (Haematocrit)
B-Erythrocytes, number concentration
B-Plattulocytes (Thrombocytes), number concentration
Platelet functions
P-Platelet aggregation
P-Prothrombin time
P-Activated partial thromboplastin time
Pt-Bleeding time
P-Fibrinogen (M_r 340 000), substance concentration
Bone marrow studies: Morphological examination
P,S-Iron, substance concentration
P,S-Ferritin, mass concentration
P,S-Transferrin, mass concentration
P-Antithrombin III, substance concentration
P,S-Vitamin B_{12} (Cobalamin), substance concentration
B,S-Folates, substance concentration

Liver

P,S-Alanine aminotransferase, catalytic activity concentration
P,S-Aspartate aminotransferase, catalytic activity concentration
P,S-Bilirubin (and conjugated), substance concentration
P,S-Alkaline phosphatase, catalytic activity concentration
P,S-γ-Glutamyltransferase, catalytic activity concentration
P,S-5'-nucleotidase, catalytic activity concentration
P,S-Protein, mass concentration and electrophoresis
P-Coagulation factors
P,S-Bile acids, substance concentration

Muscle

P,S-Creatine kinase (isoenzymes), catalytic activity concentration

Kidney

dU-Carbamide (Urea), substance concentration
dU,U-Creatininum (Creatinine), substance concentration
– Glomerular function
  Creatinine clearance
  U-Protein electrophoresis
– Tubular function
  U-Low molecular weight (M_r < 15000) proteins, substance concentration
Urinary enzymes
dU-Volume
U-Density (Osmolality)
Routine urinalysis
Routine urinary cytological examination

Lipids

P,S-Cholesterol, substance concentration
(fPt) P,S-Triglycerides, substance concentration
P,S-Lipoprotein electrophoresis
P,S-Apolipoproteins, mass concentrations

Bone

P,S-Calcium (II) (Ca), substance concentration
dU-Calcium (II) (Ca), amount of substance
P,S-Phosphate (P, non-esterified), substance concentration
dU-Phosphate (P), amount of substance
P,S-Alkaline phosphatase, catalytic activity concentration
S-Vitamin D (calciol), substance concentration

Hormones

P,S-Cortisol, substance concentration
P,S-Aldosterone, substance concentration
P,S-Thyroxine, substance concentration
P,S-Free thyroxine, substance concentration
P,S-Triiodothyronine, substance concentration
P,S-Free triiodothyronine, substance concentration
P,S-Prolactin, substance concentration
P,S-Insulin, substance concentration
P,S-Renin/Angiotensin, substance concentration
S-Growth hormone, substance concentration

Enzyme induction and pharmacogenetics

P,S-γ-Glutamyltransferase, catalytic activity concentration
dU-6β-hydroxycortisol, substance concentration
P,S-active drug and its metabolites, substance concentrations
Debrisoquine test (monooxygenation)

Immune function

P,S-Immunoglobin A, mass concentration
P,S-Immunoglobin G, mass concentration
P,S-Immunoglobin M, mass concentration
P,S-Complement (C_{3a}, C_4), mass concentrations
(T and B) Lymphocytes

Hypersensitivity

B-Eosinophil Leukocytes, number concentration
P,S-Total and specific Immunoglobulin E, mass concentrations
P,S-Anti-DNA antibodies, mass concentrations
P,S-Anti-drug antibodies, mass concentrations

3.2 Phase III

The selection of laboratory tests depends upon the results previously obtained. Observation of enzyme induction or hypersensitivity during Phase I and II clinical trials may necessitate the inclusion of certain specific clinical laboratory tests during these trials (Table 2).

Drug interactions which could alter the metabolism or toxicity of the drug should also be considered during the development of clinical laboratory testing strategies.

3.3 Phase IV

Phase IV clinical trials include elements of Phase I, II, and III clinical trials depending upon the objectives set for the specific post-marketing study being conducted. Choice of laboratory tests accordingly will vary with the objective of the clinical trial being conducted and will reflect factors found to be altered during clinical trials.

4. Conclusions and recommendations

To improve the effectiveness of clinical laboratory investigations and to facilitate the dissemination of results, the following steps should be taken:

4.1

Summary and evaluation of clinical laboratory test results should be performed after each clinical trial to identify the effects of the drug studied on laboratory tests. Also, the evaluation should contain the significant variations observed, the intensity and correlation with subject status (healthy volunteer or patients categorized by disease) according to the duration of treatment as well as drug doses administered.

4.2

Data banks should be constructed to make available results previously obtained during clinical trials. Since the results are of significant clinical relevance, they should be collected and circulated to medical scientists and practitioners.

4.3

Study groups should be formed to periodically review and update the lists of tests and their interpretation criteria to improve assessment of the risk to benefit ratio. Ultimately, these study groups would assist the development of clinical research protocols using uniform and systematic clinical laboratory methodology.

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Drug Interferences and Drug Effects in Clinical Chemistry

Part 7. Data Banks

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Preface

This paper is the seventh of a series of Recommendations on Drug Interferences and Drug Effects in Clinical Chemistry. Others deal with:

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1. Introduction

Information concerning the influences of drugs on laboratory tests is large and rapidly growing and can be found in many different scientific publications. The amount of this information as well as its variety and wide distribution render any classification or use of these data impossible without the aid of a computer (3, 4).

1.1

Data banks are needed to get reliable information in a practical form.

- As relevant data must be easily and freely accessible, a data base system is best suited for storage.
- The data information should be available interactively via data terminals.
- It should be possible to include information from the data bank into local computers and into routine hospital work.
- Abstracts from the data bank may be published at intervals. For this purpose, computerized photocomposition or other techniques without reprinting are well suited.

1.2

The following are the potential users and should be involved in the construction of the data banks.

- Clinical chemists
- Clinicians
- Pharmacists
- Drug manufacturers
- Professionals running registers for adverse drug reactions
- Health educators
- Reagent and instrument manufacturers

1.3

All drugs should be in International Nonproprietary Name (INN) but with proprietary names available.

2. Sources of information

2.1

Already existing literature and registers:

There are several collections of information published on data banks (5–11). In USA, the first data bank on this topic was completed at the National Institutes of Health in the 1970's (5). In Sweden, the Department of Drugs, National Board of Health and Welfare has collected and evaluated reports in SWEDIS, the computerized Swedish drug information system (7, 8). It contains clinically relevant information on drug interferences and effects in clinical chemistry. In France, Intermedic has been supported by "Institute National de la Sante et de la Recherche Medicale" and the Center for Preventive Medicine (Nancy-Vandœuvre). It is distributed by Societe Francaise de Biologie Clinique "Telematique systeme" and contains evaluated information on physiological variations and drug effects (9). In Great Britain, Delta Bank offers critically evaluated information on drugs and other factors which influence the interpretation of diagnostic laboratory tests (10). Some information is currently available, internationally through on-line services, from the electronic publishers Data-Star (11). Data bank information can also be obtained from the registers of drug manufacturers, and reagent and instrument manufacturers.

2.2

Information and laboratory test results performed during toxicological studies in animals and drug trials in humans.

2.3

Post-marketing surveillance of a drug.

2.4

Reports on side (adverse) drug reactions in routine clinical work:

Adverse drug reactions are sometimes detected by laboratory tests. It is essential that the relationship between the suspected drug and the adverse reaction is well documented. Adverse drug reactions are critically reviewed and excellently summarized in "Meyler's Side Effects of Drugs" by *Dukes* (12), and the uniform annuals of it. Another book containing important and well documented information on side effects of drugs is published by *Davies* (13). In many countries, adverse drug reactions are systematically collected by health authorities (14).

In the future, information from INIDIS (the International Drug Information System) of the WHO Collaborative Centre for International Drug Monitoring may be included. This system includes at present 170 000 reports on adverse drug reactions from 2 countries. However, permission from WHO is needed before the data can be made available. One limitation is that at present, only a small percentage of the clinical cases of side effects of drugs is reported. Problems in this field have been reviewed by *Colombo & Tognoni* (15).

2.5

Health examinations of patients and normal individuals.

3. Selection of reports

In order not to corrupt the data banks, it is important to include only a reasonable amount of information that is reliable and documented. The information should be judged by specially trained persons who act as an interface between published reports and data banks. In this way, it will be possible to create "knowledge banks."

3.1

The clinical significance of the variation must be proven. Quantitative aspects of drug effects on laboratory test results must be considered as discussed by *Dawkins & Salway* (13).

The reports must contain documentation on:

The probability that a particular effect will occur; the magnitude of the change induced; the precision and if possible accuracy of the analytical methods used; the clinical significance of the variation found; as well as the statistical methods used and how they were adapted to the problem.

3.2

We propose that the following types of reports, when relevant, should be stored in special data files.

- Reports concerning isolated cases. Cases of earlier unknown side effects must be analyzed, registered and grouped to detect a secondary effect affecting only a small part of a large population.
- Reports concerning overdoses of drugs.
- Intended effects obtained by drug treatment (e. g. lowering of blood glucose by insulin).
- Animal studies.
- The influence of additives (such as citrate, heparin or ethylene diamine tetracetic acid, EDTA) to the blood collection tubes.

4. General requirements of the data bank

A data base system best suited to fulfil the present and future needs of different users concerning drug effects in clinical chemistry must be adapted. The following are general requirements:

- The data base should have capability of expansion and it could be modified without altering existing programs.
- Different users should be able to use the existing data in different ways, and for new purposes.
- The data bank should be capable of exchanging information with other systems.

5. Contents of the data bank

General rules for acceptance and inclusion of information in data banks are:

- Primary publications documenting reactions to drugs should always be preferred.
- Secondary publications should not be accepted without valid supporting documentation. Information about a drug in a primary literature reference may be changed to the point of inaccuracy in secondary literature. Therefore precautions must be taken when including secondary information.

Reports concerning the following types of effects of drugs on laboratory test results should be included.

5.1

Analytical interferences (in vitro) of drugs (if possible after administration of therapeutic doses to humans).

As stated in Part 2 "Guidelines for evaluation of analytical interference" there are special problems concerning in vitro interference of drugs:

- Different analytical methods are used in different laboratories. Interferences may be of different nature, chemical or instrumental. Also small analytical modifications may be important. Thus, a detailed description of the techniques used must be available from the reference source.
- The analytical techniques are changing all the time, therefore techniques should be specified.
- A metabolite or component of the excipients of a tablet or capsule, rather than the drug itself, may be responsible for the effects. This is of particular interest in urine analysis.
- Co-administration of two or more drugs may produce different interferences.

5.2

Biological effects of therapeutic doses of drugs in vivo.

Details are found in Part 3 "Evaluation of Biological Effects of Drugs." Considerations must be given to:

- Effects observed regularly in humans
- Effects obtained in certain genetically sensitive patients
- Effects due to idiosyncrasy

5.3

Drug effects on reference values and reference limits.

5.4

Clinical relevance is a priority

- In vitro experiments are not always relevant in clinical practice (e. g., ascorbic acid affects urine glucose determination with reduction methods after in vitro addition but only in rare cases with high-dose vitamin therapy).
- Many drug effects may be statistically significant but are unlikely to be clinically relevant.
- Information for use in clinical practice should be included in data banks.
- Animal experiments can sometimes be misleading for evaluation of drug effects in humans. They are generally used as predictors of toxicity.

6. Conclusions

Data banks containing clinically important information on drug interferences and drug effects in clinical chemistry are strongly needed due to the large number of data in this field. Information on therapeutic drug effects on clinical laboratory tests is available in several disciplines. It is necessary for people working in all relevant fields to learn from each other. We certainly need collaboration between clinical chemists, haematologists, pharmacologists, clinical pharmacologists, pharmacists, drug producers, biochemists and clinicians. The task of establishing a reliable data bank on drug interferences and effects in clinical chemistry is enormous and world wide collaboration is needed.

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